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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,417	03/30/2004	Po-Ying Chan-Hui	131.03US	5640
33603 7590 04/11/2007 MONOGRAM BIOSCIENCES 345 OYSTER POINT BLVD SOUTH SAN FRANCISCO, CA 94080			EXAMINER GODDARD, LAURA B	
			ART UNIT	PAPER NUMBER
			1642	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		04/11/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/813,417

Applicant(s)

CHAN-HUI ET AL.

Examiner

Laura B. Goddard, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2007.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4 and 5 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1,2,4 and 5 is/are rejected.
7) ☒ Claim(s) 1 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 10 January 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed January 10, 2007 in response to the Office Action of July 12, 2006, is acknowledged and has been entered. Previously pending claims 1, 2, 4, and 5 have been amended. Claims 3, and 6-45 are canceled. Claims 1, 2, 4, and 5 are currently being examined.

It is noted that Applicants amended claims to exclude the elected and examined species of Her2-Her2 complexes and amended claims to recite Her1-Her2, Her2-Her3, or both complexes to change the scope of the invention.

Specification

2. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, including proper reference to applications that have been issued or abandoned. For example, application Ser. No. 10/623,057 filed 17 July 2003 **is now US Patent 7,105,308**.

Claim Objections

3. Claim 1 is objected to because of the following informalities: The claims recites "a method of diagnosing the presence of breast cancer comprising the steps of: measuring directly in a patient sample....wherein the amount of Her1-Her2 complexes, or Her2-Her3 complexes or both, indicates the presence of breast cancer in a patient". The preamble and conclusion do not match in that the preamble does not require

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detecting the presence of breast cancer **in a patient**. For consistency within the claim, Examiner suggests amending the claim to "a method of diagnosing the presence of breast cancer **in a patient**". Appropriate correction is required.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method of diagnosing the presence of breast cancer in a patient comprising measuring in a patient breast tissue sample an amount of Her1-Her2complex, Her2-Her3 complex or both, comparing each such amount to its corresponding amount in a reference normal breast tissue sample, wherein the patient breast tissue sample is a fixed tissue sample or a frozen tissue sample** does not reasonably provide enablement for a method of diagnosing the presence of breast cancer comprising measuring in **any sample** from a patient **including circulating epithelial cells** and comparing it to **any reference sample**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification discloses that a "sample" or "patient sample" means a collection of similar cells obtained from a tissue of a subject or animal. The source of the tissue sample may be a solid tissue, blood, or any body fluids (p. 13, lines 21-33). The specification discloses that a "reference sample" means one or more cell, xenograft, or tissue samples that are representative of a normal or non-diseased state. The reference sample may be from the same kind of tissue as that of the patient sample, or it may be from different tissue types (p. 12, line 29 through p. 13, line 2). Examples 2 and 10 of the specification disclose the detection of Her1-Her2 and Her2-Her3 heterodimers in breast tissue lysates or frozen tissues from human breast cancer patients, wherein a

significant number of the breast cancer specimens had an increase in the amount of Her1-Her2 and Her2-Her3 heterodimers as compared to normal tissue amounts (p. 47, lines 10-19; Figures 5A-5C; p. 59, lines 5-10; Figures 14A and 14B).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for assaying **any patient sample** and comparing it to **any reference sample**. The specification discloses the detection of Her1-Her2 and Her2-Her3 complexes in *breast tissue samples* and compares levels of the complexes to levels found in *normal breast tissue*. The specification does not provide a nexus between the diagnosis of breast cancer and the detection of said Her complexes in any other patient samples compared to any other reference samples as broadly encompassed by the claims. Those of skill in the art recognize that the diagnosis of cancer in a specific tissue such as breast tissue requires comparison to the normal counterpart tissue for control purposes.

Further, the specification does not provide a nexus between the diagnosis of breast cancer and the detection of said Her complexes in circulating epithelial cells. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials

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(see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4). Without a nexus provided between the diagnosis of breast cancer and the increased presence of said Her complexes in circulating epithelial cells as compared to

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a normal counterpart sample, one of skill in the art could not predictably diagnose breast cancer comprising practicing the claimed method.

Therefore, in view of the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for Her complex detection in all patient samples or circulating epithelial cells and comparison to all reference samples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Maintained Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 2, 4, and 5 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. **10/813412**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of Application No. **10/813412** are drawn to a method of determining disease status of a patient suffering from a disease characterized by aberrant expression of one or more Her receptor heterodimers comprising measuring directly in a patient sample an amount of each of one or more Her receptor heterodimers, comparing each such amount to its corresponding amount in a reference sample, and correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient which are an obvious variant of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented (see section 9 of the previous Office Action).

6. All other rejections recited in the Office Action mailed July 12, 2006 are hereby withdrawn.

7. **Conclusion:** No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

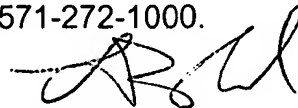
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Laura B Goddard, Ph.D.
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Art Unit 1642



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